FILE 'MEDLINE' ENTERED AT 05:00:33 ON 13 NOV 2007
L1 4369 S CCR5
L2 347 S L1 AND STRUCTURE
L3 0 S L2 AND (PM-1 OR SUPT1)
L4 285 S L2 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L5 125 S L4 AND SEQUENCE
L6 11 S L5 AND PY<1998
L7 718 S L1 AND ANTAGONIST?
L8 10 S L7 AND PY<1998
L9 10 S L8 NOT L6

FILE 'WPIDS' ENTERED AT 05:22:41 ON 13 NOV 2007
L10 596 S CCR5
L11 201 S L10 AND ANTAGONIST?
L12 167 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13 0 S L12 AND PY<1998

FILE 'USPATFULL' ENTERED AT 05:23:40 ON 13 NOV 2007
L14 2776 S CCR5
L15 1857 S L14 AND ANTAGONIST?
L16 1576 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L17 236 S L16 AND CCR5/CLM
L18 72 S L17 AND ANTAGONIST?/CLM
L19 62 S L18 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)

97327540. PubMed ID: 9184207. **HIV**-1-induced cell fusion is mediated by multiple regions within both the viral envelope and the CCR-5 co-receptor. Bieniasz P D; Fridell R A; Aramori I; Ferguson S S; Caron M G; Cullen B R. (Howard Hughes Medical Institute, Department of Genetics, Duke University Medical Center, Durham, NC 27710, USA.) The EMBO journal, **(1997 May 15)** Vol. 16, No. 10, pp. 2599-609. Journal code: 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Although the human hCCR-5 chemokine receptor can serve as a co-receptor for both M-tropic (ADA and BaL) and dual-tropic (89.6) strains of **human immunodeficiency virus** type 1 (**HIV**-1), the closely related mouse mCCR-5 homolog is inactive. We used chimeric hCCR-5-mCCR-5 receptor molecules to examine the functional importance of the three extracellular domains of hCCR-5 that differ in **sequence** from their mCCR-5 equivalents. While this analysis revealed that all three of these extracellular domains could participate in the functional interaction with **HIV**-1 envelope, clear differences were observed when different **HIV**-1 strains were analyzed. Thus, while the ADA **HIV**-1 isolate could effectively utilize chimeric human-mouse CCR-5 chimeras containing any single human extracellular domain, the BaL isolate required any two human extracellular sequences while the 89.6 isolate would only interact effectively with chimeras containing all three human extracellular sequences. Further analysis using hybrid **HIV**-1 envelope proteins showed that the difference in co-receptor specificity displayed by the ADA and BaL isolates was due partly to a single amino acid change in the V3 loop, although this interaction was clearly also modulated by other envelope domains. Overall, these data indicate that the interaction between **HIV**-1 envelope and CCR-5 is not only complex but also subject to marked, **HIV**-1 isolate-dependent variation.

97053783. PubMed ID: 8898197. Regions in beta-chemokine receptors **CCR5** and CCR2b that determine **HIV**-1 cofactor specificity. Rucker J; Samson M; Doranz B J; Libert F; Berson J F; Yi Y; Smyth R J; Collman R G; Broder C C; Vassart G; Doms R W; Parmentier M. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia 19104, USA.) Cell, **(1996 Nov 1)** Vol. 87, No. 3, pp. 437-46. Journal code: 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.

AB Macrophage-tropic (M-tropic) **HIV**-1 strains use the beta-chemokine receptor **CCR5**, but not CCR2b, as a cofactor for membrane fusion and infection, while the dual-tropic strain 89.6 uses both. **CCR5**/2b chimeras and mutants were used to map regions of **CCR5** important for cofactor function and specificity. M-tropic strains required either the amino-terminal domain or the first extracellular loop of **CCR5**. A CCR2b chimera containing the first 20 N-terminal residues of **CCR5** supported M-tropic envelope protein fusion. Amino-terminal truncations of **CCR5**/CCR2b chimeras indicated that residues 2-5 are important for M-tropic viruses, while 89.6 is dependent on residues 6-9. The identification of multiple functionally important regions in **CCR5**, coupled with differences in how **CCR5** is used by M- and dual-tropic viruses, suggests that interactions between **HIV**-1 and entry cofactors are conformationally complex.

97477421. PubMed ID: 9334377. Interaction of chemokine receptor **CCR5** with its ligands: multiple domains for HIV-1 gp120 binding and a single domain for chemokine binding. Wu L; LaRosa G; Kassam N; Gordon C J; Heath H; Ruffing N; Chen H; Humblias J; Samson M; Parmentier M; Moore J P; Mackay C R. (LeukoSite, Inc., Cambridge, Massachusetts 02142, USA.. lijun_wu@leukosite.com) . The Journal of experimental medicine, **(1997 Oct 20)** Vol. 186, No. 8, pp. 1373-81. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB **CCR5** is a chemokine receptor expressed by T cells and macrophages, which also functions as the principal coreceptor for macrophage (M)-tropic strains of HIV-1. To understand the molecular basis of the binding of chemokines and HIV-1 to **CCR5**, we developed a number of mAbs that inhibit the various interactions of **CCR5**, and mapped the binding sites of these mAbs using a panel of **CCR5**/CCR2b chimeras. One mAb termed 2D7 completely blocked the binding and chemotaxis of the three natural chemokine ligands of **CCR5**, RANTES (regulated on activation normal T cell expressed and secreted), macrophage inflammatory protein (MIP)-1alpha, and MIP-1beta, to **CCR5** transfectants. This mAb was a genuine **antagonist** of **CCR5**, since it failed to stimulate an increase in intracellular calcium concentration in the **CCR5** transfectants, but blocked calcium responses elicited by RANTES, MIP-1alpha, or MIP-1beta. This mAb inhibited most of the RANTES and MIP-1alpha chemotactic responses of activated T cells, but not of monocytes, suggesting differential usage of chemokine receptors by these two cell types. The 2D7 binding site mapped to the second extracellular loop of **CCR5**, whereas a group of mAbs that failed to block chemokine binding all mapped to the NH2-terminal region of **CCR5**. Efficient inhibition of an M-tropic HIV-1-derived envelope glycoprotein gp120 binding to **CCR5** could be achieved with mAbs recognizing either the second extracellular loop or the NH2-terminal region, although the former showed superior inhibition. Additionally, 2D7 efficiently blocked the infectivity of several M-tropic and dual-tropic HIV-1 strains in vitro. These results suggest a complicated pattern of HIV-1 gp120 binding to different regions of **CCR5**, but a relatively simple pattern for chemokine binding. We conclude that the second extracellular loop of **CCR5** is an ideal target site for the development of inhibitors of either chemokine or HIV-1 binding to **CCR5**.

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97248644. PubMed ID: 9092481. Potent inhibition of HIV-1 infectivity in macrophages and lymphocytes by a novel **CCR5 antagonist**. Simmons G; Clapham P R; Picard L; Offord R E; Rosenkilde M M; Schwartz T W; Buser R; Wells T N; Proudfoot A E. (Virology Group, Chester Beatty Laboratories, Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, UK.) Science (New York, N.Y.), **(1997 Apr 11)** Vol. 276, No. 5310, pp. 276-9. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB The chemokine receptors CXCR4 and **CCR5** have recently been shown to act as coreceptors, in concert with CD4, for human immunodeficiency virus-type 1 (HIV-1) infection. RANTES and other chemokines that interact with **CCR5** and block infection of peripheral blood mononuclear cell cultures inhibit infection of primary macrophages inefficiently at best. If used to treat HIV-1-infected individuals, these chemokines could fail to influence HIV replication in nonlymphocyte compartments while promoting unwanted inflammatory side effects. A derivative of RANTES that was created by chemical modification of the amino terminus, aminooxypentane (AOP)-RANTES, did not induce chemotaxis and was a subnanomolar **antagonist** of **CCR5** function in monocytes. It potently inhibited infection of diverse cell types (including macrophages and lymphocytes) by nonsyncytium-inducing, macrophage-tropic HIV-1 strains. Thus, activation of cells by chemokines is not a prerequisite for the inhibition of viral uptake and replication. Chemokine receptor **antagonists** like AOP-RANTES that achieve full receptor occupancy at nanomolar concentrations are strong candidates for the therapy of HIV-1-infected individuals.